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(54) Title: MEDICAMENTS FOR THE TREATMENT OF VISCERAL PAIN AND MIGRAINE (57) Abstract <p>The invention relates to the use of those 5-HT₃ receptor antagonists, which are active in the Rat Model of Colo-rectal Distension at a dose determined as the dose at which 5-HT₃ receptor antagonist activity is observed in standard tests, such as the Bezold-Jarisch model, in the treatment of visceral pain, such as the pain symptoms of IBS, and also migraine.</p>		

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MEDICAMENTS FOR THE TREATMENT OF VISCERAL PAIN AND MIGRAINE

5 This invention relates to the use of certain compounds which are 5-HT₃ receptor antagonists as visceral analgesics.

EP-A-279512 (Beecham Group p.l.c.) describes the use of certain 5-HT₃ receptor antagonists, including granisetron (KYTRIL) in the treatment of visceral pain.

10 Visceral pain is a symptom of irritable bowel syndrome (IBS) and granisetron has been found to desensitise the rectum in IBS patients as shown by double-blind placebo-controlled studies, at doses of 120 µg/kg and 50 µg/kg, 120 µg/kg being most effective. (Prior and Read, 1990; Gut 31 (10) A1174).

15 Granisetron has been found to be active in an animal model of rectal sensitivity to distension (see method described hereafter).

5-HT₃ receptor antagonists which have the same effect as granisetron in this model, include zatosetron (Lilly) and metoclopramide.

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The invention therefore relates to the use of those 5-HT₃ receptor antagonists, which are active in the animal model at a dose determined as the dose at which 5-HT₃ receptor antagonist activity is observed in standard tests, such as the Bezold-Jarisch model, in the treatment of visceral pain, such as the pain symptoms of IBS, and also
25 migraine.

Preferred compounds are active at a lower dose than the 5-HT₃ receptor antagonist dose. Compounds which are approved or under clinical investigation are active at a similar dosage level to that which is used for antiemetic use.

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Suitable modes of administration, formulations, etc. are as described in EP-A-279512.

5-HT₃ receptor antagonists which should be considered for this invention include
35 those specifically and generically disclosed and referenced in EP-A-450757 (Glaxo Group Limited).

Rat Model of Colo-rectal Distension

- A 6-7 cm latex balloon was inserted intra-anally into male Wistar rats (250-650g) under halothane anaesthesia; the balloon catheter was taped to the tail. After recovery the animals were allowed unrestricted movement and were dosed with either vehicle (saline) or 5-hydroxytryptophan (5-HTP 10mgkg⁻¹ subcutaneously). At 5 min post-dose a ramp inflation of the colo-rectal balloon was carried out for approximately 10-30s until the visceromotor threshold (abdominal muscle contraction) was observed; the stimulus was then immediately removed and threshold pressure noted. This inflation procedure was repeated at 5 min intervals. 5-HT₃ receptor antagonists or saline were dosed subcutaneously after 3 stable responses were achieved and within 45 min of dosing 5-HTP or vehicle. The visceromotor threshold values were then recorded for a further 30 min. A similar model was described by Ness & Gebhart (1988, Brain Res. 450, 153-169). Maximum percentage changes (within the 30 min post-dose period) in distension pressure were compared with the mean of the pre-dose recordings. Saline control values were then assigned the value of 1.00 and drug induced changes compared directly.
- Saline vehicle had no effect on the visceromotor threshold, whilst the dose of 5-HTP caused a reduction in the distension pressure required to elicit a response to the noxious stimulus (mean reduction of $30.7 \pm 4.4\%$). Thus, by using a dose of 5-HTP that did not cause dramatic increases in gut secretion, the rat colo-rectum could be sensitised to colo-rectal distension.
- Addition of saline after a pre-dose of 5-HTP had no effect on the decrease in threshold pressure caused by 5-HTP. By comparison, it was found that some, BUT NOT ALL, 5-HT₃ receptor antagonists when administered after 5-HTP dose dependently raised the visceromotor threshold above pre-dose values, thereby displaying a reduction in the sensitivity of the sensitized colo-rectum and producing analgesia to noxious levels of visceral distension. The Table shows the differences between selected 5-HT₃ receptor antagonists. Note that those antagonists that are active as visceral analgesics all display bell-shaped dose effect curves.

COMPOUND	DOSE	INDEX	SEM
	$\mu\text{g/kg}^{-1}$		
saline	-	1.00	0.27
5-HTP	10 000	-1.63	0.23
granisetron	1	2.17	0.40
	10	4.18	0.59
	100	2.86	0.66
	1000	2.17	0.37
	10 000	2.00	0.69
tropisetron	10	1.31	0.33
	100	1.77	0.73
metoclopramide	1	1.88	0.35
	10	2.69	0.43
	100	2.15	0.65
BRL 46470	1	0.46	0.38
	10	1.50	0.32
	100	0.02	0.28
	1000	0.55	0.39
E5*	1	2.54	0.87
	10	4.31	0.60
	100	1.79	0.56
ondansetron	10	1.03	0.15
	100	0.94	0.20
	1000	0.44	0.24
	10 000	1.61	0.49
zatsetron	1	2.73	0.77
	10	3.55	0.44
	100	2.66	0.55

*Example 5 of EP-A-377967

Thus it can be seen that granisetron, E5 and zatsetron are visceral analgesics (increasing threshold values above control by > 4-fold) falling within the invention.

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Intrathecal administration of granisetron (100mg) also showed good analgesic activity suggesting that a site of action, of those 5-HT₃ receptor antagonists that are visceral analgesics, may be in the spinal cord. Furthermore, recent evidence from neonatally capsaicin treated rats, where there is c-fibre deafferentation, suggests the presence of

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these 5-HT₃ receptors on primary afferent fibres or a role for these receptors in sensory processing mediated by capsaicin sensitive afferents.

Claims

1. A method for the treatment and/or prophylaxis of visceral pain, in mammals, including humans, which method comprises administering to the mammal in need of such treatment and/or prophylaxis, an effective and/or prophylactic amount of a 5-HT₃ receptor antagonist, which is active in the animal model at a dose determined as the dose at which 5-HT₃ receptor antagonist activity is observed in standard tests, such as the Bezold-Jarisch model.
2. The use of those 5-HT₃ receptor antagonists, which are active in the animal model at a dose determined as the dose at which 5-HT₃ receptor antagonist activity is observed in standard tests, such as the Bezold-Jarisch model, in the treatment of visceral pain.
3. A pharmaceutical composition for use in the treatment and/or prophylaxis of visceral pain, which comprises a 5-HT₃ receptor antagonist, which is active in the animal model at a dose determined as the dose at which 5-HT₃ receptor antagonist activity is observed in standard tests, such as the Bezold-Jarisch model, and a pharmaceutically acceptable carrier.
4. A method, use or composition according to claim 1, 2 or 3 wherein the compound is active at a lower dose than the 5-HT₃ receptor antagonist dose.
5. A method, use or composition according to claim 4 for the treatment of the pain symptoms of IBS.
6. A method, use or composition according to claim 5 for the treatment of also migraine.
7. A method, use or composition according to claim 1, 2 or 3 wherein the 5-HT₃ receptor antagonist is selected from those specifically and generically disclosed and referenced in EP-A-450757 (Glaxo Group Limited).
8. A method, use or composition according to claim 1, 2 or 3 wherein the 5-HT₃ receptor antagonist is granisetron.
9. A method, use or composition according to claim 1, 2 or 3 wherein the 5-HT₃ receptor antagonist is zatsetron (Lilly) or metoclopramide.